

### **Remarks**

Claims 1-12 are pending. In view of the following remarks, Applicants respectfully request reconsideration and allowance of the pending claims 1-12.

### **Claim Rejections - 35 U.S.C. §103:**

Claims 1-12 are rejected under 35 U.S.C. §103(a) as being unpatentable over AMIDON (WO 2004/010998) in view of ARZENO (WO 1997/27198), DRUG MONITOR, HANCOCK, STANIFORTH (U.S. Patent No. 6,660,303), and VALENTINE (U.S. Patent No. 5,427,799) and as evidenced by SHARMA (U.S. Publication No. 2007/0129385) and the definition of crystallization by the Encyclopedia Britannica.

Applicants would like to bring to the Examiner's notice that AMIDON (WO 2004/010998) specifically describes sustained release tablets of sumanirole maleate, pramipexole dihydrochloride monohydrate or reboxitine succinate (see Examples 3-9, 11 on Pages 30-36). Besides, AMIDON discloses about 250 or so other active pharmaceutical agents with one or more of salts (see Pages 7-14). AMIDON does not mention or recognize amorphous valganciclovir hydrochloride, which can crystallize over time, if special precautions are not taken while handling and in storage. AMIDON does not even hint anywhere about this problem of stability, leave alone discuss any means to overcome such a problem. Rather, AMIDON describes compositions that exhibit sustained-release properties and highlights the advantages of sustained release over conventional immediate release dosing (see page 1, paragraph [0005]; page 2, paragraph [0009])). Hence, it is clear that AMIDON does not disclose or even suggest the presently claimed dry process for the preparation of stable solid dosage forms comprising amorphous form of valganciclovir hydrochloride. There is therefore, no reason why one of ordinary skill in the art would be motivated to develop a dry process for the preparation of stable immediate release dosage forms of amorphous valganciclovir as described in the instant invention.

The Examiner further states that teachings in view of ARZENO, DRUG MONITOR, HANCOCK, STANIFORTH and VALENTINE teach the claimed process and "[A] general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." (See *In re Woodruff*, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990)). Applicants

respectfully disagree and would like to stress that based on these cited prior art, a person skilled in the art would not at all have recognized any need for formulating the amorphous form of valganciclovir hydrochloride by a dry process to form stable dosage forms as stated in the instant invention. *Ref. MPEP 2143.01 (I), obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006).* The applicants would again state that DRUG MONITOR does not say anywhere that there was any problem with the bioavailability of valganciclovir. It merely states the effect of food on bioavailability. HANCOCK provides a general discussion on the choice of crystalline and amorphous systems as a means to enhance dissolution and bioavailability. It does not discuss about any specific product, including valganciclovir hydrochloride. Moreover, as also pointed out earlier, though amorphous form may improve solubility and bioavailability, but, the issue of stability and any related inter-conversion between the forms becomes paramount in this case. HANCOCK (see page 2, first column, first paragraph) in fact identifies the problem associated with amorphous forms. Amorphous materials are generally thermodynamically unstable and have well-recognized inherent stability problems with a tendency to convert to crystalline form, unless handled and stored under special conditions. Moreover, polymorph conversion can occur not only during the shelf life of the formulation, but also during the formulation process. Applicants recognized from reports that the amorphous form of valganciclovir hydrochloride is metastable and might have a propensity to transform to the crystalline form during various processing steps unless specific steps to avoid it are taken. The present invention helps in formulating the otherwise difficult-to-formulate amorphous valganciclovir hydrochloride into an acceptable solid dosage form while simultaneously preventing any polymorph conversion. In the present invention, Applicants have successfully and advantageously utilized the dry process for preparation of an acceptable stable solid dosage form of amorphous valganciclovir hydrochloride wherein the amorphous form does not convert to crystalline form and the resultant dosage form has desirable tablet properties. To the contrary, none of the prior art documents cited by the Examiner provides a person ordinarily skilled in the art any suggestion or motivation to develop a dry process for the preparation of stable solid dosage forms that comprise amorphous form of valganciclovir hydrochloride.

Examiner in the office action (page 5) states that the Applicants argue the process of their invention results in amorphous valganciclovir hydrochloride which is fine, fluffy and of relatively low bulk and tap density. Applicants respectfully state that Examiner's perception is not correct. Instead, applicants have found, as mentioned in the instant specification (paragraph [0005]), that amorphous valganciclovir hydrochloride is a very fine and fluffy material, with relatively low bulk and tap density that makes it difficult to formulate into an acceptable dosage form. The challenge here was to develop a stable dosage form of amorphous valganciclovir hydrochloride with uniformity of weight, sufficient hardness and friability and other desirable tablet properties. As such, such materials are difficult to formulate using dry processes, as achieving desirable content uniformity, hardness, friability etc. is difficult. In the present invention, applicants have successfully and advantageously utilized the dry process for the preparation of stable dosage forms of amorphous valganciclovir hydrochloride wherein the amorphous form does not convert to the crystalline form and the resultant dosage form has desirable tablet properties.

With regard to ARZENO, Applicant would like to stress that ARZENO is in fact teaching away from the use of amorphous valganciclovir hydrochloride. On page 39, lines 1-3, ARZENO specifically mentions that the use of crystalline form has many advantages over the non-crystalline form. The Examiner has made an assumption based on the process steps that are being followed in ARZENO in view of SHARMA, that ARZENO may not necessarily yield crystalline form. However, ARZENO nowhere explicitly discloses amorphous valganciclovir hydrochloride. Further, ARZENO uses a mixture of water and isopropanol for purification of valganciclovir hydrochloride via crystallization (page 48, last paragraph, line 32). This is further evidenced by the disclosure by NESTOR (U.S. 6,083,953) which discloses preparation of crystalline valganciclovir hydrochloride (column 23, line 59 through column 24, line 8) as cited in ARZENO. In NESTOR, the end product valganciclovir hydrochloride is crystallized from water and isopropanol mixture to get the crystalline product. Thus, it can be said with certainty that ARZENO valganciclovir hydrochloride is in crystalline form and, with no disclosure or evidence to the contrary, there is no reason to believe that it discloses an amorphous material. Therefore, it is requested that rejection of claims with respect to ARZENO be withdrawn.

Examiner also states that with regard to rejection of claims 3-6, the technique taught by VALENTINE is used to produce sustained release formulations and the composition of AMIDON is a sustained release formulation. However, applicants would like to emphasize again that neither AMIDON nor VALENTINE teaches amorphous valganciclovir hydrochloride, which, as discussed above, has the problem of conversion to crystalline form over time. AMIDON and VALENTINE, either alone or in combination, in no way identify the problem of stability. The Examiner also states that claims 3-6 are not directed to stability of valganciclovir. Applicants respectfully submit that this is not a correct conclusion. Claims 3-6 relate to process for the preparation of stable valganciclovir hydrochloride solid dosage form, as they depend from, and thus incorporates all the limitation present in, claim 1, which clearly states that the process results in a stable dosage form, wherein the solid dosage form does not show conversion of amorphous valganciclovir hydrochloride to crystalline valganciclovir hydrochloride after storage for two months at 40°C and 75% relative humidity. The examiner is therefore requested to withdraw this rejection.

With regard to claim 8, Examiner states that it would be obvious to have modified the method taught by AMIDON by substituting with microcrystalline cellulose because the method utilized by AMIDON is a direct compression method and microcrystalline cellulose is a direct compression tableting excipient which is generally considered to exhibit superior compressibility and disintegration properties as taught by STANIFORTH. Applicants would like to assert again that neither AMIDON nor STANIFORTH discloses amorphous valganciclovir hydrochloride, neither recognizes any problem related to its stability and the process for its formulation as identified in claim 8, which depends from claim 1 and thus incorporates all the limitation present in claim 1. The examiner is therefore requested to withdraw this rejection.

The Office action concludes that invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by references. However, to conclude applicants would like to mention that none of the cited references discloses amorphous valganciclovir hydrochloride; nor do they discuss the stability problems associated with it. None of these references suggests that using a dry process would provide the needed solution for the problems associated with amorphous valganciclovir hydrochloride. In the present case, Applicants have recognized the problem and have

successfully invented a process for formulating the same into an acceptable solid dosage form. Applicants respectfully assert that the currently amended claim 1 is not obvious in view of the cited references. Dependent claims 2-12 are likewise not obvious in view of the cited references for the same reason. In view of the above remarks, Applicants respectfully request withdrawal of rejections under 35 U.S.C. §103 and issue allowance of claims 1-12.

### **Conclusion**

For the reasons stated above, the Examiner is urged to allow claims 1-12 to issue. Authorization is hereby given to charge any fees deemed to be due in connection with this Response to Office Action to Deposit Account No. 50-0912.

Respectfully submitted,

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